# SUPERFUND BASIC RESEARCH AND TRAINING PROGRAM

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## PURPOSE OF THIS RFA

The mission of the National Institute of Environmental Health Sciences (NIEHS) is to promote research that will ultimately reduce the burden of human illness and dysfunction from environmental causes. Complementary to this mission are the goals of the national Superfund Program, established by Congress in 1980 to: identify uncontrolled hazardous wastes; characterize the impacts of hazardous waste sites and emergency releases on the surrounding environment (i.e., communities, ecological systems, and ambient air, soil, water); and, institute control or remediation approaches to minimize risk from exposure to these contaminants. With the 1980 passage of the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), better known as Superfund, it soon became clear that the strategies for the cleanup of Superfund sites, and the technologies available to implement these cleanups, were inadequate to address the magnitude and complexity of the problem.

In 1986, the NIEHS Hazardous Substances Basic Research and Training Program [the Superfund Basic Research Program (SBRP)] was created under the Superfund Amendments and Reauthorization Act (SARA). Congress, under SARA, authorized NIEHS to develop a university-based program of basic research and training grants to address the wide array of scientific uncertainties facing the national Superfund Program. The assignment of the SBRP to the NIEHS underscored an emphasis on human health effects, evaluation and prevention. However, the Program was mandated to support research that moved beyond the biomedical arena. Inclusion of non-traditional NIH research such as the modeling of fate and transport processes and the development of remediation technologies for environmental contaminants became part of a new paradigm for environmental health research. This paradigm supports the philosophy that the long-term improvement of public health will require the integration of biomedical, geological and engineering sciences to develop and apply a full range of primary prevention strategies. Therefore, the SBRP, supports coordinated multi-project, multidisciplinary university-based programs that link biomedical research with related engineering, hydrogeologic and ecologic research.

The scientific parameters under which the SBRP operates were included in the SARA legislation, which mandates that the research funded by this Program should include development of (1) methods and technologies to detect hazardous substances in the environment; (2) advanced techniques for the detection, assessment, and evaluation of the effect on human health of hazardous substances; (3) methods to assess the risks to human health presented by hazardous substances; and (4) basic biological, chemical, and physical methods to reduce the amount and toxicity of hazardous substances.

Accordingly, NIEHS is proposing the continuation of the SBRP to address these mandates. Grants made under the SBRP will be for coordinated, multi-project, multi- and interdisciplinary programs. The objective remains to establish and maintain a unique Program that links and integrates biomedical research with related engineering, hydrogeologic, and ecologic components.

In addition, the SBRP is committed to the concept that the Program is more than just a basic research program, and that to truly be effective it must foster the training of graduate and post doctoral students and be proactive in translating the scientific accomplishments emanating from the Program to its stakeholders -- whether to the public through community outreach, to industry via technology transfer, or to government through partnerships. Therefore, NIEHS has included training, community outreach and the translation of research to appropriate audiences as components of this solicitation.

[Note: Within this document the use of the word “Program” with an uppercase "P" is used to denote the SBRP, whereas “program” with a lower case "p" denotes the research program of the individual applicant.]

DESCRIPTION OF THE SBRP

The SBRP was created as a network of multidisciplinary, interdisciplinary teams of researchers to address the broad, complex health and environmental issues that arise from the multimedia nature of hazardous waste sites. Assembling researchers from diverse disciplines to focus on a unifying theme has provided the opportunity to advance the science in a more effective, efficient and resource-leveraged manner. Furthermore, establishing multidisciplinary research programs provided a more comprehensive understanding of complex environmental issues. The knowledge gained through these research efforts has proven useful in supporting the decisions made by state, local, and federal agencies, private organizations and industry

related to the management of hazardous substances.

In addition to supporting multidisciplinary, interdisciplinary research, the SBRP has considered community outreach, training of graduate students and post-doctoral candidates, and the translation and communication of its research findings to be important in realizing the full potential of the Program.

Presently, the Program funds 19 university-based grants, for a total of 234 research projects and support cores (http://www-apps.niehs.nih.gov/sbrp/index.cfm). There are 70 collaborating universities and institutions associated with these 19 programs. This current solicitation marks the second round of competition for the SBRP as it implements its plan for phasing the Program from a competition held once every five years for five-year awards, to an annual competition for up to five-year awards. The overall intent of this change is to enhance the ability of the SBRP to be more responsive to emerging issues by taking advantage of new and promising technologies as they arise to address the complexities associated with exposure to hazardous substances. This change will also provide the scientific community more opportunities to compete for SBRP funding and the ability to revise and resubmit applications in a timely fashion.

Because the SBRP is a large continuing program, altering the competition cycle from once every five years to an annual competition is a complex undertaking. To implement this change in a logical and systematic manner necessitates that there be a distribution of new and competing applications submitted. Accordingly, half of the existing programs submitted applications under RFA ES-04-001 and the remaining half of the programs will submit applications under this solicitation. New and revised applications will also be accepted.

RESEARCH OBJECTIVES

Background

The management of hazardous waste sites is one of the most challenging environmental issues facing the United States. Thousands of hazardous waste sites exist, including Superfund sites (considered the nation’s most seriously contaminated sites), as a result of decades of industrial development, mining, manufacturing and military activities. Contamination of soils, sediments and groundwaters at these sites represents a significant potential threat to human and ecological health. In 1980, legislation was enacted (CERCLA) to address the cleanup of these sites. However, it became clear shortly thereafter, that the strategies for the cleanup of Superfund and hazardous waste sites, and the technologies available to implement these cleanups, were inadequate to address the magnitude and complexity of the problem.

Many factors contribute to the complexity of the problem faced at sites. Hazardous waste sites contain a large number of toxic chemicals such as polycyclic aromatic hydrocarbons (PAHs), other chlorinated organics and metals. Though there are examples where only one or two contaminants may be found at a site, more often hundreds of different chemicals will be found at a single site, having known, and in many cases, unknown toxicities. Moreover, the physical, chemical and biological characteristics of soils, sediments or ground water at waste sites are important factors for understanding the chemical transformation and movement of hazardous substances through these environmental medias, and, ultimately, the potential for exposure to humans and ecosystems. Adding to the environmental complexities at a site, are the community issues, such as peoples’ concerns about health effects and the

communication of hazards, both of which may impact the decision-making process. Furthermore, decisions necessary to develop effective cleanup plans at one site may not be applicable to other sites, making the magnitude of the nation's cleanup effort even more difficult. With this realization, Congress in 1986 with the passage of SARA, established the SBRP as a university-based grants program at NIEHS, an institute of the NIH, to develop a basic research and training program that complements the activities undertaken by the U.S. Environmental Protection Agency (EPA, http://www.epa.gov/superfund/index.htm), the principal manager of the Superfund Program and the Agency for Toxic Substances and Disease Registry (ATSDR, http://www.atsdr.cdc.gov).

To ensure that the SBRP meets the programmatic goals of the national Superfund Program and complements the needs of EPA and ATSDR, the research investment made by the SBRP must be "accountable", that is the research supported by the Program must provide a fundamentally sound science base for sister Superfund Program's "applied" objectives. For example, although the biomedical research conducted within the SBRP is not inherently different from biomedical research supported by other NIEHS programs, its uniqueness is the fact that the research should lead to its application in the risk assessment process, and, therefore, is "accountable." In contrast, the non-biomedical (e.g., hydrogeology, geochemistry, engineering, ecology, etc.) research is unique to the NIEHS. There are no other NIH or NIEHS programs that support these sciences in the context of improving site characterizations and providing informed cleanup decisions. The integration of biomedical, geochemical and engineering knowledge acquired through the Program provides "accountability", and should advance both the understanding of the human and ecological risks from hazardous substances, as well as the development of new environmental technologies for the characterization and cleanup of sites. As a consequence, more informed risk assessment and remediation decisions could be achieved, resulting in lower cleanup costs and the development of a range of primary prevention strategies for improving public health, ecosystems and the environment.

A conceptual framework that has guided the SBRP is one that encompasses a holistic approach to environmental health sciences and basic research, i.e., the long-term improvement of public health requires an interdisciplinary approach that integrates biomedical, geochemical and engineering sciences. Decisions that are needed to protect human health, ecosystems and the environment must be based on mechanistic knowledge gained from the integration of available data from all relevant research disciplines such as toxicology, molecular biology, epidemiology, geology, ecology and engineering.

For example, it is important to understand the consequences of exposure to environmental agents on human health and the relationship between exposure and disease outcome, as well as the effect of exposures on ecosystem dynamics. From a scientific perspective, a holistic approach involves contributions from all research disciplines. For example, identifying chemical contaminants; assessing properties that may affect transport and bioavailability of contaminants; and determining the critical pathways that result in exposures to human populations or ecosystems requires incorporating tools and approaches utilized by engineering, geochemical, biomedical and ecologic specialties. Understanding the potential health consequences involves not only assessing the levels and timing of exposure and whether the substance has reached a target organ or cell, but also determining whether contaminant exposure results in changes in normal physiologic processes, which could lead to disease or dysfunction or changes in biodiversity/ecological succession. Identifying the intrinsic (e.g., genetic) and host (e.g., nutrition, health, lifestyle habits) factors that may lead to

enhanced sensitivity or resistance in a subset of the population are important considerations in developing human and ecological risk assessments.

Prevention strategies to minimize exposures that could affect human or ecosystem health require the development and application of appropriate remediation technologies. While remediation strategies and technologies have been approved for cleanup at many Superfund sites, questions remain as to the effectiveness and appropriateness of these technologies for the long term. Moreover, remediation methods that are appropriate for one site may be inappropriate for other sites. Therefore, fundamental research focused on site characterization is important. Site characterizations influence the selection and application of a remediation strategy. Elucidating the biological, chemical and physical characteristics of a site and integrating this knowledge with an understanding of the molecular, physical or chemical processes involved in various remediation strategies will provide opportunities for the continued development of newer and more effective remediation approaches that will enhance our ability to protect human health and ecosystems. An emerging issue that may arise from the use of new remediation strategies is the potential of unforeseen adverse effects on ecosystems, human health and the environment. This complexity emphasizes the importance for interactions among engineers, toxicologists and other health and wildlife specialists.

Clearly integration from many different disciplines will be needed to address these complex, interdependent yet fundamental issues. The relationships among these issues are difficult to address. However, with the rapidly emerging development of new and sensitive methodological tools, some of these interactions are being defined with increased precision and sophistication. Continued development of exposure models, remediation methods, development and validation of biomarkers of exposure, effect and susceptibility based on mechanistic data, and the application of these to epidemiological and ecological studies will be important for risk assessment and in the decision making process for developing better and more effective remediation and/or containment strategies.

Research goals and objectives

As the legacy of human activity continues to expand, biomedical research and environmental and engineering sciences must act in close partnership to address the complex environmental challenges of the future. For the past 16 years, the NIEHS has encouraged and fostered partnerships among the diverse disciplines of science by creating, through the SBRP, multi-project, multidisciplinary programs each of which is focused on a central theme. However, until recently, strong interdisciplinary research, which brings different scientific disciplines together to study a common hypothesis, has been hampered by limitations in technologies. Technological advances such as “omics” technologies (genomics, proteomics, metabonomics, etc.); molecular, cellular and whole animal imaging methodologies; miniaturized tools/technologies (i.e., at the micro and nano-level); and improved cyber-infrastructure and bioinformatic tools to gather, assimilate and interrogate large diverse datasets, have the capacity to stimulate interdisciplinary research.

Thus, the goals and objectives of this RFA are to encourage the use of technological advances, as appropriate, to support multi-project, interdisciplinary research programs. The intent of applying these technologies is to enhance risk assessment and remediation decisions by improving our understanding of the health and environmental consequences associated with contaminants found at hazardous waste sites, and to develop improved strategies and technologies for cleaning up these sites. It is

expected that each interdisciplinary research program will develop an overall conceptual theme that fosters collaborative interactions, whereby projects are integrated, and specific emphasis is placed on interactions between the biomedical and non-biomedical research projects. Such interactions promote synergistic knowledge, which has the potential to: (1) improve our understanding of the relationship between exposure and disease; (2) promote the development of a range of primary prevention strategies, (3) translate into lower cleanup costs, and (4) allow for the refinement of human and ecological risk assessments. All are important goals of the SBRP.

As stated previously, the NIEHS considers research supported by the SBRP to be an accountable enterprise. This accountability derives from the supposition that the evolution and maturation of hypothesis-driven basic research leads to increased opportunities for the translation of results into applied, “product-oriented” research directions. It is this evolution combined with the integration of biomedical and non-biomedical research within a thematic framework that allows for environmental synthesis and its application to real-life problems facing the nation’s cleanup efforts. The knowledge gained through these efforts, ultimately, should reduce the burden of human illness and dysfunction from environmental causes. Therefore, the scientific themes and the research topics included in research proposals submitted by applicants should be cognizant of, and reflect the mandates and goals of the SBRP.

A central premise of the SBRP is that there is a link between chemical exposure and disease outcome, and that understanding/identifying this link will help to establish new or improved prevention/intervention modalities. Therefore, the Program's approach emphasizes basic and applied research, using state-of-the-art techniques, to improve the sensitivity and specificity for detecting adverse effects in humans or in ecosystems exposed to hazardous substances. In addition, the Program emphasizes understanding the phenomena that affect transport, fate and transformation of hazardous substances, and developing remediation strategies that attenuate and mitigate exposure as necessary to protect human and ecological health.

The scientific topics that are appropriate for this RFA to meet the goals and the objectives of the Program basically cover almost all aspects of scientific and intellectual inquiry and methodology that are directly related to understanding the relationship between exposure to hazardous substances and human health, impacts of hazardous substances on ecosystems, and strategies to understand the physical, chemical and biological processes affecting chemicals in environmental media as well as methods and approaches to effectively reduce the amount and toxicity of hazardous substances. However, for the purposes of the RFA, this research must be in context of the chemicals considered appropriate for study. These include:

o Hazardous substances found with some frequency at Superfund sites.
o Hazardous breakdown products of such substances formed in environmental media by physical, chemical or biological (e.g., plants, microorganisms, etc.) processes.
o Hazardous metabolites of the above substances or their breakdown products formed in humans or experimental animals.
o Chemicals with structural similarity to hazardous substances found at Superfund sites.

Note also that the applicant may refer to these Web sites to obtain information on hazardous substances that are relevant to Superfund and to USEPA (http://www.epa.gov/superfund/resources/chemicals.htm) and ATSDR (http://www.atsdr.cdc.gov/clist.html).

Rather than provide detailed lists of research topics and approaches that are appropriate for study, examples of broad scientific themes relevant to the SBRP will be discussed. These thematic examples are meant to stimulate the thinking of potential applicants by illustrating interdisciplinary linkages between scientific disciplines, and, ultimately, how this knowledge enhances public and environmental health. These examples are not intended to be exhaustive, and investigators may study these and many other topics that meet the objectives of the RFA. The applicant is also directed to the following site (http://www-apps.niehs.nih.gov/sbrp/rfa/resources.html) for additional research topics and approaches of interest to the SBRP.

Mechanism-based Research

Understanding the mechanisms whereby toxicants induce adverse health effects is at the heart of the SBRP. It is believed that the environment plays a contributing role in the etiology of most human diseases/dysfunctions (e.g., reproductive, immune competence, pulmonary/cardiovascular, cancer, neurodevelopment, neurobehavioral, renal, etc.). Therefore, research is needed that attempts to explain biologically complex systems in the context of exposure to environmentally relevant concentrations of hazardous substances and health outcome, by simplifying to a level where the problem is tractable. This typically results in moving from whole animal and organ-level biology to the powerful "cellular" and "molecular" approaches, and as these processes are understood by applying them back to whole animal and organ-level research.

An important consequence of supporting basic research to determine the underlying mechanism(s) responsible for environmentally induced diseases, is the identification of biomarkers – key molecular or cellular events that link a specific environmental exposure to a health outcome. The SBRP has a long-standing commitment to supporting research focused on the development, validation and application of biomarkers for use in population-based studies. It is believed that as biomarkers become validated they will be invaluable in the prevention, early detection and early treatment of disease.

Therefore, the SBRP seeks to support mechanistic research that includes laboratory-based studies unraveling disease pathways at the molecular and cellular level to the organ and whole animal level, as well as human-based and ecosystem-based mechanistic studies. The development and validation of biomarkers and their application in human and ecological studies is also encouraged. In addition to traditional methodological approaches, the use of state-of-the-art technologies and their integration should be considered as applicable. Examples include:

o Micro/nano –arrays
o “Omics” approaches (genomics, proteomics, metabonomics, etc.)
o Imaging technologies (molecular, cellular, etc.)

At another level, knowledge accumulated through the more traditional analytical reductionist framework primarily used within the SBRP, has provided useful systematic descriptions of biological systems. However, the limitations of this reductionist approach in gaining a deep understanding of physiologic conditions and diseases associated with chemical exposure are becoming apparent. For example, even when using current state-of-the-art molecular approaches there remains an inability to appraise 'biological noise'. This inability leads to focusing on a few genes, transcripts and proteins subject to major detectable changes, rather than small fluctuations that may be major determinants of the behavior of biological systems. Accordingly, the SBRP seeks to support research that surmounts these difficulties by encouraging a new, "integrative" biology.

This “integrative” or systems level approach seeks to understand the structure and dynamics of regulatory networks within biological systems to better understand the mechanistic underpinnings of disease risk. Systems biology involves the creation of “virtual” (in silico) models of biological systems that are grounded in a molecular-level understanding to define and study the structure and dynamics of biological processes. Research is encouraged to develop new approaches to bring together existing data from experimental approaches (e.g., genetics, genomics, proteomics, metabonomics) and to integrate the data with hypotheses using mathematical and computational approaches. This may include building models through an iterative process of observation, modeling, hypothesis formulation or knowledge discovery and simulation-based analysis and verification. It is anticipated that deciphering functional genomics within an organismal context for systems biology will rely heavily on transgenics and genetics utilizing genetic models to achieve knowledge.

Susceptibility and Predisposition Research

A critical confounding factor underlying the physiological consequences of exposure to hazardous substances is susceptibility. Susceptible populations may be defined as having unique characteristics that make them more sensitive to the effects of exposures to contaminants or other external insults. The Program recognizes the importance of identifying susceptible populations in order to reduce their burden of environmentally induced diseases. To address this issue, the SBRP seeks to support research focused on understanding the influence of intrinsic factors (e.g., genetic polymorphisms, haplotypes, gender and age), host factors (e.g., nutrition, health, lifestyle habits), and timing of exposure on cellular functions (e.g., metabolic capacity, repair of DNA damage, cell proliferation and apoptosis) critical to altering susceptibility and predisposition to disease. Not only is enhanced susceptibility an issue, but also understanding factors that contribute to an individual’s resistance to effects of exposure are important considerations. The knowledge gained from understanding the interrelationships of factors in affecting host susceptibility and resistance will be key to reducing uncertainties in risk assessments and protecting health for the most vulnerable populations.

Translating these research findings and adapting appropriate molecular tools for use by epidemiologists in the conduct of population-based research is also a high research priority for the SBRP and is encouraged. Integration of these approaches into population-based studies has the potential to enhance the power to observe associations between exposure and health, or cause and effect relationships. The management, analysis and interpretation of complex and diverse data sets that emerge from these studies will require the development of new biostatistical approaches and mathematical algorithms to understand gene-environment, gene-gene or multi-gene-environment interactions. This will necessitate the collaborative efforts of biologists, epidemiologists, statisticians, systems engineers, computer scientists and others for integrating the available information from animal and human studies in such a manner that would inform the risk assessment process.

Exposure Assessment Research

A priori, an environmentally induced disease implies that exposure has occurred within some temporal, spatial framework in relation to the appearance of disease. As such, there should be a direct link between exposure and disease morbidity and mortality. Unfortunately, as important as exposure is to the disease paradigm, it is one of the most difficult parameters to measure. Because exposure assessment is so integral to

decisions related to protecting human health and ecosystems, understanding the complexities that impact the exposure component is an important research focus for the SBRP. One of the factors that contribute to this complexity is site characterization. Site characterization is an integral component of the exposure assessment paradigm because of the potential for humans and ecosystems to be exposed to contaminants at hazardous waste sites. Therefore, it is critical to understand the nature of contaminants found at a site, the potential for transformation and migration, and eventual uptake by humans and wildlife.

The SBRP seeks to support research that improves site characterization so that the knowledge gained can be incorporated into the exposure assessment paradigm. Examples of research topics include methods to (1) identify and quantify chemical forms of the contaminants; (2) determine the toxicity of the contaminants, the concentrations of contaminants, the location of contaminants within a site, the ability of the contaminants to be chemically or biologically transformed; and (3) assess the physical, chemical and biological factors that affect movement of these contaminants from the site. The development and application of new and advanced technologies such as biosensors, self-contained miniaturized toxicity-screening kits and miniaturized analytical probes and data analysis tools that allow for real-time, on site monitoring, is encouraged. The resulting data can then be placed in context of how contaminants affect nearby populations -- human or wildlife.

Another factor that interacts directly with both exposure assessment and site characterization is bioavailability. Bioavailability of a contaminant describes the degree to which it is available for transformation, and transport within environmental medias (i.e., soil, sediments and surface and ground water) as well as the degree by which a contaminant eventually is assimilated by organisms. As an integrating principle, bioavailability crosses all scientific disciplines and is an important factor to consider in understanding the fate and transport of hazardous substances; the ability of hazardous substances to be internalized by microbes, wildlife and humans; and the ability once internalized to be available to tissues and organs. Accordingly, the SBRP considers research in these areas to be appropriate and of interest.

The integration of available data from site characterization and bioavailability studies into exposure and risk assessment models provides a means to predict potential exposure levels in human populations and ecosystems. The validation of these models requires the development and application of new methods and technologies that can measure the extent of exposure in these disparate populations. Many approaches are available that have the requisite sensitivity and specificity to detect current exposures, or measure contaminants that have a long half-life in biological systems. However, the issues of past exposures and exposure to mixtures are still intractable problems. For example, rarely is one exposed to a single chemical, but rather is exposed either concurrently or sequentially by various routes of exposure, to a large number of chemicals over varying periods of time. Moreover, the concentrations of contaminants found in the environment and in living systems may be at very low levels. Therefore, research activities of interest for the SBRP are the development of improved technological methods and computational approaches to study temporal and spatial factors associated with timing of exposure, and to detect and assess exposure history within the context of biological relevancy. For example, research that applies advances in miniaturization technology may provide a unique opportunity to redefine exposure assessment by improving visualization tools, detection methods (such as biosensors), analytical tools, and data mining/data analysis tools that can be used for both environmental media and

living biological systems. Research to develop mathematical, computational and statistical techniques that integrate this information into a holistic model for exposure and risk assessment is also encouraged.

Remediation Research

The SBRP has a unique function within the NIEHS, in that research is supported that goes beyond the biomedical arena. One area where this is quite evident is in the support of the application of engineering sciences as a primary prevention strategy to improve human health by mitigating exposure and reducing toxicity of environmental contaminants at hazardous waste sites through remediation. At one level, it is important to understand the scientific principles and underlying processes necessary to clean up persistent toxics in groundwaters, sediments and soils. At another level, the translation of these basic principles into efficient and cost-effective technologies is equally important. By supporting this continuum of research from basic to applied approaches, preventing exposure and mitigating risk from exposure becomes a realistic goal.

Accordingly, the SBRP encourages the development of innovative physical, chemical and biological technologies for remediating hazardous substances found at waste sites. For example, the SBRP has had a long-term investment in basic research focused on the mechanistic basis for degradation and sequestration of contaminants by microbial, as well as other biological systems. The relationships between the number and type of species found at a site, the environmental contaminants, the nutrient requirements and other factors need to be considered in developing efficient bioremediation strategies. The use of modern molecular biology tools as well as biochemical, cellular or engineering approaches to enhance our understanding of the basic structural and functional properties of microbial and other populations involved in the bioremediation of hazardous substances is encouraged.

Hazardous waste sites and Superfund sites very rarely contain a single contaminant but rather represent a complex mixture of many chemical classes at sites that may have varied physical, hydrogeochemical, or biogeochemical properties. These complexities may make the use of a single remediation strategy less effective. Research that integrates and applies mixed technologies may represent tractable approaches and is encouraged. Furthermore, advanced technologies, for example, nanotechnology and bio-engineered plants, worms and microbes, provide new opportunities for remediation research. However, the introduction of these new tools into the environment may present their own hazards. Research that simultaneously seeks to understand the impact and potential toxicity of introducing innovative approaches into the environment is a new area of research ripe for exploration.

Ecosystems Research

Understanding the ecological impacts from hazardous waste sites is a complex problem, in part, due to the number of species involved and their interdependencies. There is little baseline data describing all the components that reside within an ecosystem. Likewise, there is limited data available on the effect of various exposure scenarios on the different levels of ecosystem complexity, ranging from individual species, population levels, through ultimately the ecosystem level. Without these baseline data, it becomes extremely difficult to assess whether perturbations of the environment resulting from remediation efforts cause additional harm to the health of the ecosystem beyond that introduced by the original contaminants. In another vein, traditional ecosystem research has been done in isolation of human studies and has borrowed minimally from the advances made in this

arena. Moreover, the dynamics between these two domains has not been fully explored.

To address these issues as well as others, the SBRP seeks to support research at the interface of biology, ecology, microbiology, bioengineering and engineering sciences. Research that may be directly applicable to the use of ecosystems as natural experiments to model the consequences of bioavailability and sequestration of contaminants is an area ripe for exploration. For example, if sequestration of contaminants at a site is an acceptable remediation strategy, what are the potential exposure consequences over time as aging and weathering occurs? Ecosystem research is also a valuable tool for understanding exposure assessment by evaluating bioavailability/bioconcentration of contaminants in the food web as a basis for predicting bioavailability/bioconcentration in humans.

Ecological research would benefit tremendously by the continued application of state-of-the-art methods that have been primarily applied to human studies. For example, the development of informative “biomarkers” that identify stressors, key “sentinel” species and define the linkages between ecological genetics, stress responses within the ecosystem could draw from advances made in human biomarker studies. The SBRP encourages the application of “omics” tools, new sensor technologies and informatics with the goal of enhancing our understanding of ecological succession and biodiversity as a function of exposure to contaminants. These approaches may also provide a surrogate strategy for understanding potential human health effects.

Mixtures

A critical issue related to hazardous waste sites for remediation or health effects research is that the concentrations at which chemicals occur in the environment are extremely low and exposures are long-term, continual, with simultaneous exposure to multiple chemicals. Whether one considers remediation strategies, exposure to humans or ecosystems, site characterization, bioavailability or the development of risk assessment models, chemical mixtures are an issue of concern. Biomedical research, exposure assessments or remediation strategies based on exposures to single substances in isolation is rarely reflected in real-life scenarios. This over-simplification fails to consider (1) prior exposure history and vulnerability (i.e., susceptibility); (2) interactions from other stressors of similar/dissimilar mechanisms of action; (3) potentiation or sensitization by chemicals not toxic in themselves; and (4) interactions of chemicals that could lead to synergistic or antagonistic effects.

The SBRP seeks to support research that considers the effects of mixtures. With the continued development and refinement in the available repertoire of advanced tools and approaches, the scientific community may be in a better position to assess the impact of mixtures on all areas of research important to the SBRP. When considering research approaches for mixtures it will be critical to apply the latest technologies and mathematical approaches to investigate those biological effects that are subtle in nature and likely to escape immediate notice when using traditional approaches. The synthesis of diverse datasets to enhance our knowledge base for mixtures will be necessary to meet the challenges faced by researchers, environmental policy-makers and public health officials in designing and implementing strategies to reduce human disease and effects on ecosystems arising from exposure to mixtures.

Risk Assessment

The goal for every hazardous waste site cleanup is to protect the public’s health and the environment. The risk assessment process helps to define

exposures of concern and potential threats. The more robust the risk assessment, the better one is able to contribute to cost effective and yet protective choices. The synthesis of environmental knowledge resulting from SBRP conducted research ultimately should contribute to the robustness of the risk assessment process. Scientific inquiry that develops a paradigm whereby knowledge gained through understanding ecological effects resulting from hazardous waste sites furthers our understanding of potential human health effects, provides a creative, holistic approach to integrate seemingly separate ecological and human health risk assessments into more comprehensive site models. However, to fully realize the benefits from SBRP conducted research, especially as it pertains to issues of susceptible populations, low dose effects, mixtures and ecological studies, a new generation of risk assessment models will be required.

With the advent of the “omics” technologies, development and application of bioinformatic tools to gather, assimilate and interrogate large diverse datasets will be a necessity to fully take advantage of the knowledge that may be gained from these approaches. How this information is used within the current risk assessment paradigm is an issue for further study. In addition, bioinformatic methods are needed for the integration and interpretation of information obtained, not only by the different “omic” technologies, but also across scientific disciplines. This approach will provide the tools necessary to synergize interdisciplinary research and enhance environmental knowledge useful for risk assessment.

Therefore, the SBRP is interested in innovative research to develop new risk assessment models that incorporate these issues. In addition, the development of new bioinformatic approaches to bridge data from different disciplines is needed. For example, multi-dimensional models are needed to describe risk from the source of contamination, through the movement of contaminants within environmental media, to its uptake by biological receptors (i.e., human or wildlife) and the effect within biological receptors on complex cellular and molecular pathways to the incipience of dysfunction or disease. This will require more detailed datasets and more sophisticated methods for their interpretation and mathematical algorithms for their modeling. Moreover, as analytical detection methods improve, risk assessment models must be able to better characterize the lowest dose-response effects that are biologically relevant. This will require more sophisticated statistical and computational methodologies and improved mathematical algorithms for predictive and computational toxicology. In addition, the SBRP encourages anticipatory research and identification of “emerging” issues, especially in identifying pivotal sources of uncertainty that might affect risk estimates.

CORES

Although novel, innovative, cutting-edge research projects are the nucleus of an SBRP grant, it is the intent of the SBRP that the research activities be integrated into an interdisciplinary program. In support of this goal, NIEHS requires the establishment of cores. Each grant application is required to have an Administrative Core, a Research Translation Core, and at least one Research Support Core. Outreach and Training Cores may also be included in support of achieving a truly multidisciplinary approach to hazardous substances research.

Administrative Core

The Administrative Core is a required component of a program. This Core provides the Principal Investigator a vehicle for overseeing the following:

o Planning and Coordination of Research Activities

o Integrating Cross-Discipline Research
o Overseeing Fiscal and Resource Management
o Maintaining Ongoing Communications with NIEHS

As part of planning and coordination, the Principal Investigator provides leadership and guidance in fulfilling the stated objective of the program. To accomplish this the Principal Investigator should create within the Administrative Core an infrastructure that supports inter- and multi-disciplinary research. This infrastructure should provide an environment that promotes cross-discipline interactions among all of the projects and cores.

To support the Principal Investigator in achieving these goals, NIEHS requires that the Principal Investigator establish an external advisory committee. The advisory group would evaluate:

o the merit of the research
o the relevance and importance of the individual components to the goals of the program
o the integration of research across disciplines
o the appropriateness of outreach activities
o the effectiveness of translating research to appropriate audiences
o the effectiveness of training activities

Based on the evaluation, the committee would then make recommendations to the Principal Investigator regarding future efforts in these areas.

The external advisory committee should meet at least once annually. The composition of the committee should include appropriate scientific expertise as well as represent appropriate stakeholder interests. For example, not only should the academic community be represented on the committee, but also other stakeholders, such as industry, community or government representatives should be selected to serve on the committee.

The NIEHS anticipates that the administrative core will reflect responsibilities for fiscal and administrative management of the program.

NIEHS considers communication with SBRP associated staff to be a high priority and places this responsibility within the Administrative Core. Therefore, as part of the Administrative Core, NIEHS requires that a plan be established for ensuring the effective communication and transfer of important research findings and other program outcomes to NIEHS. This plan should include identifying a point-of-contact for NIEHS who is knowledgeable in and informed of program activities. This plan should include a direct line of communication between the Administrative Core and the Research Translation Core such that all Research Translation Core activities can be reported to SBRP program managers.

Research Translation Core

Beyond the requirement discussed in the Administrative Core of communicating research findings to NIEHS, it is equally important that the grantees actively communicate important research outcomes to appropriate audiences to ensure the accurate and timely use of data. Accordingly, NIEHS includes, as a required component, the establishment of a Research Translation Core. For the purpose of this RFA, SBRP defines Research Translation to be “communicating research findings emanating from the program in the manner most appropriate for the intended audience.” Examples of appropriate audiences are EPA Headquarters, EPA Regional Offices, ATSDR, state and local governments, health professionals, industry, etc. Under this Core, a strategy must be developed that describes how partnerships and other communication tools can

be employed to ensure that the program's research is being appropriately applied to immediate environmental and health issues. As part of this strategy, the applicant should describe opportunities for receiving feedback from the designated audience confirming the utility and appropriateness of the communication tools selected.

The SBRP envisions that this Core will be the proactive communication arm of the program. Required components of this Core are as follows:

o Partnerships with Governmental Agencies: Of paramount importance to this effort is the establishment of ongoing communication with the federal, state and/or local agencies charged with protecting human health and the environment. Each program is required to propose a plan explaining how interactions with the appropriate regional or national governmental agencies will be achieved. The intent of this is to ensure that governmental offices have first-hand access to the valuable resources the program can provide, and that the investigators have knowledge of the real and immediate needs faced by their counterparts in the public sector.

In the past, one valuable activity for some projects and cores has been to conduct research or collect samples from Superfund sites. These activities, of course, are always done in concert with appropriate site officials. If this type of activity is part of the program, the applicant should propose a method for documenting and communicating these activities as part of their plan for partnering with government agencies.

o Technology transfer: It has always been necessary and important that the research generated within a program find its way into the hands of an end-user, whether that is in the commercialization of a product or the use of that information/data in decision-making. Therefore, it is imperative that the applicant considers the ultimate use or application of the research emanating from its program. Each applicant must include in the Research Translation Core a plan for identifying opportunities for moving research findings into application. For some applicants, the plan may include formal technology transfer (i.e., application for patents), and for others, technology transfer may be conducted on a less formal basis (i.e., non-patented application of research advances -– moving research from bench scale to demonstration). Regardless of the approach, the plan should include a description of how research within the program will be identified for technology transfer and outline the anticipated steps involved in the process.

o Communicating to Broad Audiences: The applicant should consider who are the other stakeholders for his/her program, and how to ensure that these groups have timely access to research findings. Accordingly, as part of the Research Translation Core, the applicant must identify the mechanism to be used for sharing research findings and engaging important stakeholders. Examples of approaches that the applicant may develop, include, but are not limited to:

- Sponsorship of workshops, short symposia, or web-based symposium. Applicants are encouraged to incorporate opportunities for advancing their program's discoveries using this mechanism. These would typically be one-day events that are local or regional in nature and could potentially involve not only academics but also other stakeholders (e.g., industry or local or regional health departments).

- Development and use of advanced communication tools or methods such as web-based systems, geographic information systems or other technologically innovative systems.

- Development and use of more traditional communication tools such as the translation of complex research findings into print and web materials intended for the lay public based on communication best practices.

Research Support Cores

Research Support Cores are principally designed as a service or resource component to the research projects within a program. Core facilities may include laboratory and clinical facilities, biostatistics and/or bioinformatics support, and analytical equipment and services. The NIEHS requires a minimum of one Research Support Core. By definition, a Research Support Core must function to support two or more research projects. The intent of a Research Support Core is to provide centralized services that will produce an economy of effort and/or savings in overall costs. Furthermore, these cores also promote interdisciplinary activities.

Community Outreach Core

Throughout the life of the SBRP, there has always been an “Outreach” component of the Program. While the intent of this activity has consistently sought to provide the Program’s stakeholders with information emanating from SBRP in a manner and format that is useful and informative, the intended “audience” has evolved over time. At this point, the SBRP has targeted the Outreach Core specifically to Community Outreach and it is anticipated that community issues will be primarily health related in nature. However, other topics of interest to the community such as environmental concerns are also appropriate. The focus on outreach to communities positions the SBRP to support the Superfund Program’s mandate to more actively involve the community in the decision-making process.

Accordingly, NIEHS strongly recommends that programs formulate a Community Outreach Core that is designed to address this need. For the purpose of this RFA, SBRP defines community outreach to be “extending support or guidance to communities, community advocates or community organizations. Appropriate target communities include those that (1) are living in proximity to, or affected by hazardous waste sites or (2) are exposed to hazardous substances via other pathways.” For example, appropriate community groups could include local government, tribal councils, established groups/organizations focused specifically on local environmental/site issues, or community service groups focused on educating the community about local issues. As an outgrowth of this activity, it is expected that interactions with the community will also serve to enhance the program’s research agenda.

The SBRP encourages that community outreach activities be done in full partnership with the target community. In other words, the community should participate in the design and approach of the activity at the onset of the project. It is also appropriate that community outreach activities be done in conjunction with the EPA, the ATSDR, or other technical assistance programs. At the same time, it is important that the applicant ensure that their efforts do not duplicate other agencies activities.

The Community Outreach Core should build from the strengths of the research program, and offer the community expertise and knowledge that draws from the program as well as from other resources. However, if outreach involves communication to lay audiences, it is suggested that individuals be included with expertise in fields such as technical communication, risk communication, health education and promotion, or health communication to ensure quality and to avoid unintended effects.

Community outreach activities may be either very broad or very focused.

Examples that are appropriate for a Community Outreach Core are:

o Sponsoring short courses or workshops to improve the community's awareness and understanding of environmental health issues (e.g., conducting a workshop that provides information on exposure levels that may or may not pose serious health risks and why, and develop an approach for addressing the issues).

o Increasing access to relevant information and serving as a resource (e.g., responding to community's questions on cumulative risk or the need for comprehensive risk assessments, assisting them in accessing pertinent information or translating materials into the community's native language).

o Education on health and technical issues (e.g., sponsoring a short course on risk assessment, or developing health effects fact sheets).

o Establishing collaborative projects among communities, investigators and other colleagues to address environmental problems (e.g., partnering with tribes in determining exposure pathways specific and relevant to their traditional and cultural practices).

It is important that the Community Outreach Core define the approach it will use to identify a community/organizational unit with which it proposes to collaborate, and present a plan detailing the objectives and the methods (e.g. conducting small group discussion or listening sessions, producing informational materials, providing leadership mentoring, etc.) that will be used in establishing and maintaining involvement with the community. The SBRP also recognizes that any activity of this nature needs to be reviewed for lessons learned and outcomes. Accordingly, the SBRP anticipates that each Community Outreach Core should include in its plan how it will measure milestones or outcomes.

The Community Outreach Core is limited to $100,000 direct costs in the first year, with subsequent years subject to the standard cost escalations of three percent. It is expected that the Core will complement the research strengths of the program. Support for appropriate staff positions, consultants, travel and supplies are allowed. The budget must include travel to the SBRP annual meeting as it is expected that the Community Outreach Core Leaders will convene during this time.

Training Core

An area of importance to the overall performance of the Program, and to the future of environmental health research in general, is training. For the purpose of this RFA, SBRP intends that the Training Core will be used to support graduate and advanced training in environmental health, environmental sciences, ecology, and geosciences (including hydrogeology, geologic engineering, geophysics, geochemistry, and related fields) in the setting of the research program. Applicants are encouraged to propose specific plans for interdisciplinary training as part of their overall program.

The Training Core should reflect the interdisciplinary nature of the overall research effort. Of special interest is the cross training of students and post-doctoral fellows in disciplines not traditionally linked in the university structure. Students pursuing degrees in the non-biomedical areas should be encouraged to place their studies in the context of environmental health sciences and biomedical research. Likewise, students of the biomedical sciences should have cross training opportunities to learn about the non-biomedical areas of study.

In addition to providing students with unique opportunities in interdisciplinary research, the SBRP also encourages the Training Cores to

provide students with other skills that will enable these emerging investigators to be better prepared to communicate their research to diverse audiences. For example, all researchers need to know how to communicate their work in a manner easily understood by the intended audience – whether the audience be the public or professionals in other areas of science. A case-in-point is the SBRP itself. Due to its multidisciplinary nature, researchers are required to effectively communicate their research beyond the boundaries of their individual scientific discipline. Accordingly, the SBRP encourages the Training Core to provide experiences for its students in the development of effective communication skills. Another important opportunity for students is the participation in the Community Outreach Core. The SBRP encourages the Training Core to formally support cross training of this nature. Opportunities such as this will provide students with valuable insights on the full cycle of the research that they conduct.

It is important to note that the training of pre- and post-doctoral students may be carried on outside the structured Training Core. In these cases, the budgets for these students should be part of the project or core budgets rather than the Training Core budget.

In keeping with the NIH efforts to train members of minority groups, and those with disabilities, applicants are encouraged to consider these candidates in their recruitment efforts.

Individuals in the training positions must be considered employees of the institution and not trainees receiving stipends as in National Research Service Award programs. Salaries and fringe benefits consistent with institutional policies may be requested. Funds may also be requested for tuition, where appropriate, and travel to one scientific meeting per year. The direct costs of the Training Core are not to exceed six percent of the total budget.

SBRP External Guidance

The NIEHS received guidance and scientific directions in the development of this solicitation from numerous and diverse sources. Specifically, the below mentioned resources have assisted us in developing research objectives and identifying other components in the RFA. Full documents and reports detailing these interactions plus other useful information can be found at the SBRP RFA Web Page http://www-apps.niehs.nih.gov/sbrp/rfa.html. We encourage the applicant to review this site.

Guidance advocating interdisciplinary research, as presented throughout this document stems from the strong messages that the SBRP has received from the scientific community and colleagues from other federal and state agencies. In February 2003, the NIEHS convened an external workgroup to provide the SBRP with guidance on research direction and approaches. The group strongly endorsed the critical role interdisciplinary research can play in accomplishing the goals set out by the SBRP. They also advocated the use of emerging tools and technologies, as well as promoting a systems approach to addressing complex issues that hazardous waste sites present.

To ensure relevance and need, SBRP actively engaged with its colleagues in other governmental organizations prior to the formulation of the RFA. Discussions with other agencies, including the EPA and ATSDR, were particularly important in helping identify research gaps that, when filled, could assist these agencies' abilities to protect public health. Reports from some of the more recent meetings with other agencies identify not only research needs but also important suggestions for maintaining strong communication with their offices. Reports can be viewed on

http://www-apps.niehs.nih.gov/sbrp/rfa/partnerships.html.

NIEHS has an established mechanism of surveying the scientific community for identifying cutting edge science and critical gaps in the various disciplines through its sponsorship of workshops and conferences. The SBRP selects to support conferences in areas that are of high program interest that will identify emerging issues in areas of programmatic interest. Through the support of conferences, the NIEHS promotes the growth of a field and fosters interdisciplinary opportunities. Typically, meeting reports are published with specific emphasis highlighting emerging areas of scientific needs. The SBRP drew from these meetings important insights on potential future directions for the Program. For a complete listing of SBRP conferences and workshops and resultant reports and publications refer to http://www-apps.niehs.nih.gov/sbrp/Conf2000/Conf.cfm.

MECHANISM OF SUPPORT

This RFA will use the NIH multi-project (P42) award mechanism. NIEHS anticipates that it will issue a SBRP RFA annually. Applications that are not funded in the competition described in this RFA may be resubmitted as amended applications in subsequent solicitations for this Program. As an applicant you will be solely responsible for planning, directing, and executing the proposed project. The anticipated award date is April 1, 2006.

This RFA uses just-in-time concepts and the non-modular budgeting format. Applicants must use the forms for regular research grants, follow the specific instructions in the PHS 398 application kit, and provide a complete detailed budget (Forms Pages 4 & 5) with narrative justifications. This program does not require cost sharing as defined in the current NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2001/part_i_1.htm.

Grants funded under this Program must be multi-project, interdisciplinary efforts that bring together investigators from different scientific disciplines to direct discrete Research Projects, each of which is to be related to the goals of the SBRP and to a central theme developed for the applicant’s program.

In order to be considered for funding, each applicant must successfully meet the following requirements:

Requires a minimum of:

o Three approved biomedical Research Projects (e.g., mechanistic-based studies, epidemiology, human risk assessment, exposure assessment, genetic susceptibility, etc.) and,
o One approved non-biomedical Research Project (e.g., ecology, ecological risk assessment, fate and transport, hydrogeology, engineering, remediation, phytoremediation, etc.)

Historically research projects have been categorized as biomedical and non-biomedical to ensure the multidisciplinary focus for environmental health research as it relates to Superfund issues. However, the scientific community recognizes that inter-disciplinary research is necessary to advance the field. Accordingly, projects that integrate biomedical and non-biomedical aims within a single research project should be considered.

Requires an approved Administrative Core to include:
o an External Advisory Committee

Requires a minimum of one approved Research Support Core:
o A Research Support Core must provide support to two or more Research Projects.

Requires an approved Research Translation Core to include:
o A plan for Partnerships with Government Agencies
o A plan for Technology Transfer
o A plan for Communicating to Broad Audiences

It is critical that the applicant recognize that the SBRP is more than just a basic research program and the applicant should make investments in other crucial areas of the Program. Therefore, in addition to the required elements, the SBRP strongly encourages the inclusion of:
o An Outreach Core
o A Training Core

The following restrictions or caps are applicable to each program:

o The total number of Research Projects and Research Support Cores cannot exceed 12. The Administrative, Research Translation, Outreach or Training Cores do not count towards this total.

o The applicant is required to specify which projects are to be considered biomedical research and which are to be considered non-biomedical research.

FUNDS AVAILABLE

The NIEHS intends to commit approximately $24 million in FY 2006 to fund seven to ten grant applications in response to this RFA. Applicants may request a project period of up to five years. The maximum budget that can be requested is $2.1 million in direct costs for the first year. The budgets for each subsequent year may not exceed an escalation of three percent on recurring direct costs. Facilities and Administrative (F&A) costs incurred by including third party consortia or subcontracts in the application will not contribute to the $2.1 million cap in direct costs. Applications that exceed the $2.1 million direct cost cap (excluding third party F&A) will be returned as non-responsive to the RFA.

As discussed in the “Description of the SBRP” section of this RFA, the Program is transitioning from a competition held once every five years to an annual competition. In order to accomplish this transition in a timely and efficient manner, applications awarded in Fiscal Year 2006 may be funded for three, four or five years. Decisions on the length of funding will be based on technical merit, programmatic balance and availability of funds.

Although the financial plans of the NIEHS provide support for this program, the funds that are appropriated for the SBRP are determined each year according to the Federal budget process. Because the funding level of this Program may vary from year to year, awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications. The actual award levels for approved and funded applications will be based on Program balance and the availability of funds, in addition to the scientific merit considerations of the review process.

ELIGIBLE INSTITUTIONS

You may submit an application if your institution is an accredited institution of higher education. Foreign institutions are not eligible to apply.

Section 311(a)(3) of SARA limits recipients of awards to "accredited institutions of higher education," which are defined in the Higher Education Act, 20 USC (annotated) 3381. However, grantees are permitted under the law, and encouraged by NIEHS, to subcontract as appropriate with organizations, domestic or foreign, public or private (such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government) as necessary to conduct portions of the research. Examples of other organizations may include generators of hazardous wastes; persons involved in the detection, assessment, evaluation, and treatment of hazardous substances; owners and operators of facilities at which hazardous substances are located; State and local governments and community organizations.

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups, as well as individuals with disabilities are always encouraged to apply for NIH programs.

SPECIAL REQUIREMENTS

Annual Meetings: It is the intent of the NIEHS to hold annual grantee meetings under this Program. Funds for travel by appropriate staff (i.e., Principal Investigator, Business Manager, and three students) to attend a three-day meeting should be included in the Administrative Core’s budget for each year. It is also anticipated that the Outreach Core and Research Translation Core Leaders will convene at the annual meeting, and expenses for this travel should be included in their individual budgets. The location of the meeting site will rotate among the different grantees.

Quality Assurance Statement: Quality Assurance Statements will be necessary ONLY for Research Support Cores that provide analytical, quantitative services to the applicant’s program.

EPA regulations as stated in 40CFR30.54 require the inclusion of a Quality Assurance Narrative Statement (QANS, OMB # 2080-0033, approved 8/14/97) for any project application involving data collection or processing, environmental measurements, and/or modeling. The QANS provides information on how quality processes or products will be assured. NIEHS cannot consider applications incomplete without this statement, however, it requests that the QANS be included with all applications that contain analytical and quantitative cores. For awards that involve environmentally related measurements or data generation, a quality system that complies with the requirements of ANSI/ASQC E4, "Specifications and Guidelines for Quality Systems for Environmental Data Collection and Environmental Technology Programs," must be in place. The Quality Assurance Statement should not exceed two pages. This Statement should, for each item listed below, present the required information, reference the specific page and paragraph number of the project description containing the information, or provide a justification as to why the item does not apply to the proposed research.

1. Discuss the activities to be performed or hypothesis to be tested and criteria for determining acceptable data quality. (Note: Such criteria may be expressed in terms of precision, accuracy, representativeness, completeness, and comparability or in terms of data quality objectives or acceptance criteria. Furthermore, these criteria must also be applied to determine the acceptability of existing or secondary data to be used in the project. In

this context secondary data may be defined as data collected for other purposes or from other sources, including the literature, compilations from computerized data bases, or results from mathematical models of environmental processes and conditions.)

2. Describe the study design, including sample type and location requirements, all statistical analyses that were or will be used to estimate the types and numbers of samples required for physical samples, or equivalent information for studies using survey and interview techniques.

3. Describe the procedures for the handling and custody of samples, including sample collection, identification, preservation, transportation, and storage.

4. Describe the procedures that will be used in the calibration and performance evaluation of all analytical instrumentation and all methods of analysis to be used during the project. Explain how the effectiveness of any new technology will be measured and how it will be benchmarked to improve an existing process, such as those used by industry.

5. Discuss the procedures for data reduction and reporting, including a description of all statistical methods with reference to any statistical software to be used to make inferences and conclusions; discuss any computer models to be designed or utilized with associated verification and validation techniques.

6. Describe the quantitative and/or qualitative procedures that will be used to evaluate the success of the project, including any plans for peer or other reviews of the study design or analytical methods prior to data collection.

ANSI/ASQC E4, "Specifications and Guidelines for Quality Systems for Environmental Data Collection and Environmental Technology Programs," is available for purchase from the American Society for Quality, phone 1-800-248-1946, item T55. Only in exceptional circumstances should it be necessary to consult this document.

WHERE TO SEND INQUIRIES

We encourage inquiries concerning this RFA and welcome the opportunity to answer questions from potential applicants. Because of the complexity of the SBRP, applicants are strongly encouraged to contact NIEHS staff early in the grant preparation process. Inquiries may fall into three areas: scientific/research, peer review, and financial or grants management issues:

o Direct your questions about scientific/research issues to:

Claudia Thompson, Ph.D.
Center for Risk and Integrated Sciences
Division of Extramural Research and Training
National Institute of Environmental Health Sciences
P.O. Box 12233 MD EC-27
Research Triangle Park, NC 27709
Telephone: 919-541-4638
FAX: 919-541-4937
Email: thompsol@niehs.nih.gov

Beth Anderson
Center for Risk and Integrated Sciences
Division of Extramural Research and Training
National Institute of Environmental Health Sciences
P.O. Box 12233 MD EC-27

Research Triangle Park, NC 27709
Telephone: 919-541-4481
FAX: 919-541-4937
Email: tainer@niehs.nih.gov

William Suk, Ph.D., M.P.H.
Center for Risk and Integrated Sciences
Division of Extramural Research and Training
National Institute of Environmental Health Sciences
P.O. Box 12233 MC EC-27
Research Triangle Park, NC 27709
Telephone: 919-541-0797
FAX: 919-541-4937
Email: suk@niehs.nih.gov

o Direct your questions about peer review issues to:

Sally Eckert-Tilotta, Ph.D.
Scientific Review Branch
Division of Extramural Research and Training
National Institute of Environmental Health Sciences
P.O. Box 12233, EC-30
Research Triangle Park, North Carolina 27709
Telephone: 919-541-1446
Fax: 919-541-2503
E-mail: eckertt1@niehs.nih.gov

Janice Allen, Ph.D.
Scientific Review Branch
Division of Extramural Research and Training
National Institute of Environmental Health Sciences
P.O. Box 12233, EC-30
Research Triangle Park, North Carolina 27709
Telephone: 919-541-7556
Fax: 919-541-2503
E-mail: allen9@niehs.nih.gov

o Direct your questions about financial or grants management matters to:

Susan Ricci
Grants Management Branch
Division of Extramural Research and Training
National Institute of Environmental Health Sciences
P.O. Box 12233, EC-30
Research Triangle Park, North Carolina 27709
Telephone: 919-316-4666
Fax: 919-541-2860
E-mail: ricci@niehs.nih.gov

Lisa Archer
Grants Management Branch
Division of Extramural Research and Training
National Institute of Environmental Health Sciences
P.O. Box 12233, EC-30
Research Triangle Park, North Carolina 27709
Telephone: 919-541-0751
Fax: 919-541-2860
E-mail: archer@niehs.nih.gov

LETTER OF INTENT

Prospective applicants are asked to submit a letter of intent that includes the following information:

o Descriptive title of the proposed research
o Name, address, and telephone number of the Principal Investigator
o Names of other key personnel
o Participating institutions
o Number and title of this RFA

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows NIEHS staff to estimate the potential review workload and plan the review.

The letter of intent is to be sent by February 14, 2005. The letter of intent should be sent to:

Sally Eckert-Tilotta, Ph.D.
Scientific Review Branch
Division of Extramural Research and Training
National Institute of Environmental Health Sciences
P.O. Box 12233, EC-30
111 T.W. Alexander Drive
Research Triangle Park, North Carolina 27709
Telephone: 919-541-1446
Fax: 919-541-2503
E-mail: eckertt1@niehs.nih.gov

SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). Applications must have a DUN and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the Universal Identifier when applying for Federal grants or cooperative agreements. The D&B number can be obtained by calling (866) 705-5711 or through the web site at http://www.dunandbradstreet.com/. The D&B number should be entered on line 11 of the face page of the PHS 398 form. The PHS 398 document is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov

SUPPLEMENTARY INSTRUCTIONS:

As the PHS 398 is used primarily for the traditional research project grant applications, several sections of the PHS 398 must be modified and expanded to provide the additional information needed for the Superfund Basic Research and Training Program applications. Detailed guidelines to supplement the PHS instructions are provided in the "Application Guidelines for the Superfund Basic Research and Training Program" and can be found on: http://www.niehs.nih.gov/dert/rfa.htm.

INFORMATIONAL MEETINGS

The NIEHS staff held an “Applicant Information Meeting” on October 29, 2003 for prospective applicants interested in submitting an SBRP grant application. At that meeting NIEHS staff explained the purpose and research focus of the Program; provided instructions about the application and review process; and answered questions. Although an informational meeting is not

planned for this year, the web-cast version of last year's meeting is available and can be found at http://www-apps.niehs.nih.gov/sbrp/rfa/aim.html. In addition, staff (see "Where to Send Inquiries") are available to discuss any aspects of the application process.

USING THE RFA LABEL: The RFA label available in the PHS 398 (rev. 5/2001) application form must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked. The RFA label is also available at: http://grants.nih.gov/grants/funding/phs398/labels.pdf

SENDING AN APPLICATION TO THE NIH: Submit a signed, typewritten original of the application, including the Checklist, and two signed, photocopies (exclude appendix materials), in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express/courier service)

At the time of submission, three additional signed copies of the application and five copies of collated appendix materials (Appendix materials should be clearly identified and collated by project and core; do not staple or bind) MUST be sent to the NIEHS Scientific Review Administrator:

Sally Eckert-Tilotta, Ph.D.
Scientific Review Branch
Division of Extramural Research and Training
National Institute of Environmental Health Sciences
P.O. Box 12233, EC-30
79 T. W. Alexander Drive, 3rd Floor, Room 3167 (Courier/Express)
Research Triangle Park, North Carolina 27709
Telephone: 919-541-1446
Fax: 919-541-2503
E-mail: eckertt1@niehs.nih.gov

APPLICATION PROCESSING: Applications must be received on or before the application receipt date listed in the heading of this RFA. If an application is received after that date, it will be returned to the applicant without review.

Although there is no immediate acknowledgement of the receipt of an application, applicants are generally notified of the review and funding assignment within 8 weeks.

The Center for Scientific Review (CSR) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. However, when a previously unfunded application, originally submitted as an investigator-initiated application, is to be submitted in response to an RFA, it is to be prepared as a NEW application. That is, the application for the RFA must not include an Introduction describing the changes and improvements made, and the text must not be marked to indicate the changes from the previous unfunded version of the application.

PEER REVIEW PROCESS

Upon receipt, applications will be reviewed for completeness by the CSR. NIEHS staff will do an administrative review for completeness and responsiveness to the RFA. Incomplete and/or non-responsive applications will not be reviewed. The specific points of consideration to determine completeness and responsiveness are: (1) the appropriateness of the science proposed in regard to the mission of the NIEHS and the SBRP's mandates; (2) the general completeness of the application including responsiveness to programmatic requirements (as listed under "Mechanism of Support"); (3) the organizational adequacy for review (this includes both scientific and budgetary considerations); and (4) the adherence to the $2.1 direct cost ceiling (see "Funds Available").

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group (Special Emphasis Panel, [SEP]) convened by the NIEHS in accordance with the review criteria stated below. The SEP will include scientific and technical experts with the necessary proficiency to adequately review the biomedical and non-biomedical science as well as all other components of the application. Since these applications are complex and formal site visits are not planned, it is essential that all applications be thoroughly prepared and that they be well organized in accordance with the guidelines.

As part of the initial merit review, all applications will:

o Undergo a process in which only those applications deemed to have the highest scientific merit, generally the top two/thirds of the applications under review, will be discussed and assigned a priority score.
o Receive a written critique.
o Receive a second level review by the NIEHS National Advisory Environmental Health Sciences (NAEHS)Council.

Two to three weeks prior to the review meeting, the SRA will forward any questions the reviewers may have after reading the application to the PI in order to clarify outstanding issues or questions. If additional questions/issues arise during the review meeting that must be addressed by the applicant, the SRA will contact the PI by telephone during the meeting for his/her input.

It is important to note that SEP members will examine proposed budgets closely. The SEP may recommend adjustments, in the requested budgets and periods of support for the components of SBRP applications.

Submission of Additional Information by Applicants

There is a period of several months between the time of submission of the application and the initial review. In the event of substantial new findings during this interval, the applicant is encouraged to contact the SRA to seek permission to submit supplementary materials. These materials will generally not be accepted within 30 days prior to the initial scientific review. The SRA will make the final determination as to what additional information will be provided to the reviewers. Please note, this is information that the applicant wishes to include and not information being requested by the SEP members as described above.

NAEHS Council Review

The NAEHS Council makes the final review and recommendation on all scored applications. The Council has two responsibilities relating to grant applications under review: (1) it evaluates the adequacy and appropriateness

of the initial review process, and (2) it considers the significance of the application to the overall program goals of the NIEHS. Upon consideration of these issues the Council makes appropriate recommendations to the Director, NIEHS. The Council does not function as a second scientific review body.

REVIEW CRITERIA

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. Within this context, the goal of the SBRP is to improve public health by supporting integrative interdisciplinary research that includes the ability to identify, assess, and evaluate the potential health effects of exposure to hazardous waste and to develop innovative chemical, physical and biological technologies for reducing potential exposure to hazardous substances. In the written comments, reviewers will be asked to evaluate the application, as described below, in order to judge the likelihood that the integrated research and related efforts will have a substantial impact on the pursuit of SBRP goals.

The scientific review group will address and consider each of the following criteria in assigning the application’s overall score, weighting them as appropriate for each application. The application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

(A) Review Factors for the Overall SBRP Application

The scientific review panel will evaluate the inter-relationship and contributions of the research projects and cores to an overall conceptual theme and goals of the program as well as the scientific merit of the program as a whole. This includes the significance and importance of the research program to further the knowledge of environmental health sciences and the understanding of the physical, chemical and biological properties of hazardous substances in the environment and the translation and delivery of the research findings to appropriate audiences. There must be evidence of the potential for meaningful interdisciplinary collaboration between all of the components of the program. Components that are not recommended for further consideration are not included in the overall evaluation; however, such projects will reflect on the leadership capabilities of the Principal Investigator.

For a SBRP application to receive a priority score, it must consist of at least three biomedical projects, one non-biomedical project, a Research Translation Core, a minimum of one Research Support Core (each found to have significant and substantial merit) for the duration of the project period and an acceptable Administrative Core. Each Research Support Core must provide essential functions or services for at least two Research Projects.

(B) Review Factors for Renewal Applications

In addition, for competing renewal applications the following will be considered:

o Progress and achievements specific to this program since the previous competitive review and the documentation through publications, conferences, etc., that demonstrates that collaboration between or among projects has occurred.

o Previous performance and estimated use of the core(s).

o Justification for adding new projects or cores or for deleting components previously supported.

o Prior commitment to transferring research findings to appropriate audiences such as EPA, EPA Regions, ATSDR, State and local professionals or other professionals working in the field of hazardous waste management.

(C) Review Factors for the Research Projects

The review of the individual Research Projects is similar to the review of investigator-initiated individual project grant applications (R01). Accordingly, these projects must have substantial scientific merit. Reviewers will evaluate the individual projects against five review criteria. The four technical review criteria (Significance, Approach, Innovation and Environment) are intended to encourage reviewers to focus on the global impacts of each project, rather than concentrating on the experimental details and their critiques. The review criteria are as follows:

SIGNIFICANCE: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

APPROACH: Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

INNOVATION: Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

INVESTIGATOR: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

ENVIRONMENT: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

For competing renewals, reviewers will evaluate whether previous specific aims, as funded, have been accomplished and that the new research goals are logical extensions of ongoing work.

Additionally, reviewers will evaluate each project for its contribution to the overall goals of the SBRP application:

o Scientific merit of each individual project in the context of the proposed programmatic theme, (i.e., assessment of the importance of the ideas or aims, the rationale and originality of the approach, the feasibility of the methods and the value of the result).

o Specific scientific objectives of each project that will benefit significantly from, or depend upon, collaborative interactions with other projects in the program (i.e., objectives that can be uniquely accomplished, specific contributions to the accomplishments of objectives in other projects, objectives that can be accomplished with greater effectiveness

and/or economy of effort, etc.).

In addition to the review criteria described above for research projects, the following will be considered by the SEP in evaluating the cores, the multidisciplinary and interdisciplinary nature of the program and the principal investigator (sections D-J).

(D) Review Factors for the Research Support Cores

o Overall use of each core. Does each Research Support Core provide essential facilities or service for two or more of the Research Projects judged to have substantial scientific merit? Is the projected use sufficient to warrant establishment of the core?

o Are the core facilities contributing to the overall research activities of the program?

o Are the requests for equipment, supplies and other items to support the activity of the core appropriate and justified?

o Is there a plan to prioritize core usage?

o Is the Quality Control and Quality Assurance plan for cores that are providing quantitative analyses adequate?

o Are the personnel involved in the core qualified and do they have the appropriate experience and level of commitment?

o For competing renewals, have the previous specific aims, as funded, been accomplished?

(E) Review Factors for the Administrative Core

o Lines of authority and the administrative structure to manage a multi-project program. Does the program’s internal plan promote coordination of interdisciplinary research, stimulate collaborations among constituent Research Projects and Cores, and evaluate research productivity? Is there a decision-making process for the management of funds and resources? Is there an ability to provide administrative support to the project and core leaders?

o External advisory committee. Is there an appropriate plan to establish and use an external advisory committee? Do the members of the committee have the expertise required to evaluate all projects and cores and appropriately represent the applicant’s stakeholders?

o Are the senior leaders of the administrative core qualified and have they demonstrated effective and responsible leadership in the past? Is the percent effort requested adequate?

o Are the qualifications, duties and percent efforts of administrative staff appropriate to contribute to the needs and conduct of the program’s research activities?

o Is there a plan to coordinate and exchange information with SBRP staff?

o Are the resources committed to the Administrative Core adequate?

(F) Review Factors for the Research Translation Core

o Are the proposed personnel qualified to conduct the activities described

for the Core?

o Is the proposed plan to partner with governmental agencies adequate?

o Is the proposed plan to identify technology transfer opportunities appropriate?

o Communication with broad audiences adequate. Is there adequate commitment and support for the approach being developed? Are the communication tools selected appropriate for the intended audience?

o Are the resources committed to the Research Translation Core adequate for the proposed activities?

(G) Review Factors for the Community Outreach Core

o Is the proposed approach appropriate, adequate and feasible?

o Is there sensitivity to socioeconomic and cultural factors and have these been adequately addressed?

o Are the plans adequate for coordination and collaboration with appropriate community groups, and state, local and federal agencies?

o Do the core members have appropriate qualifications and experience to fulfill the goals of the outreach core?

(H) Review Factors for the Training Core

o Objectives, design, and direction of the research-training program. Are the approaches and methods used adequate to develop training curriculum and courses that provide opportunities to interface with different scientific disciplines? Does the training program reflect the interdisciplinary nature of the program?

o Are the plans for the recruitment and selection of individuals participating in the Training Core appropriate?

o Adequacy of the training environment. Is there institutional commitment? Are the quality of the facilities and the availability of courses appropriate to the SBRP? Is there an availability of research support for post-doctoral training?

o For competing renewals, have the previous specific aims, as funded, been accomplished?

(I) Review Factors for the Multidisciplinary and Interdisciplinary Nature of the Program

o Interdisciplinary nature of the proposed research activities. Is there integration of the projects around a central theme? Are there plans to effectively pursue interdisciplinary research objectives?

o Synergy of the program. Is the whole greater than the sum of the parts? Is the size of the program sufficient to afford effective interaction focused on a specific central theme, but diverse in scientific disciplines in order to achieve meaningful contributions to protecting human health and the environment?

o Is there evidence of integration and interaction of the non-health related

research with the health-based research as it contributes to the central theme of the program?

(J) Review Factors for the Principal Investigator

o Does the Principal Investigator have the necessary leadership and scientific experience to effectively direct a large complex multidisciplinary program?

o Does the Principal Investigator demonstrate an appropriate level of commitment and have the ability to develop a well-defined central research focus?

o Does the Principal Investigator demonstrate the appropriate ability and experience to coordinate the interactions of the Research Projects with effective utilization of cores to achieve programmatic goals?

ADDITIONAL REVIEW CRITERIA: In addition to the above criteria, the following items will be considered in the determination of scientific merit and the priority score:

PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISK: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed. (See criteria included in the section on Federal Citations, below).

INCLUSION OF WOMEN, MINORITIES AND CHILDREN IN RESEARCH: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated. (See Inclusion Criteria in the sections on Federal Citations, below).

CARE AND USE OF VERTEBRATE ANIMALS IN RESEARCH: If vertebrate animals are to be used in the project, the five items described under Section f of the PHS 398 research grant application instructions (rev. 5/2001) will be assessed.

SHARING RESEARCH DATA: Applicants requesting $500,000 or more in direct costs in any year of the proposed research must include a data sharing plan in their application. The reasonableness of the data sharing plan or the rationale for not sharing research data will be assessed by the reviewers. However, reviewers will not factor the proposed data sharing plan into the determination of scientific merit or priority score. (for NIH instructions and policy see http://grants.nih.gov/grants/policy/data_sharing/index.htm).

BUDGET: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research.

RECEIPT AND REVIEW SCHEDULE

Letter of Intent Receipt Date: February 14, 2005
Application Receipt Date: April 21, 2005
Peer Review Date: October 2005
Council Review: February 2006
Earliest Anticipated Start Date: April 1, 2006

AWARD CRITERIA

Award criteria that will be used to make award decisions include:

o Scientific merit (as determined by peer review).
o Availability of funds.
o Programmatic priorities.

REQUIRED FEDERAL CITATIONS

ANIMAL WELFARE PROTECTION: Recipients of PHS support for activities involving live, vertebrate animals must comply with PHS Policy on Humane Care and Use of Laboratory Animals (http://grants.nih.gov/grants/olaw/references/PHSPolicyLabAnimals.pdf), as mandated by the Health Research Extension Act of 1985 (http://grants.nih.gov/grants/olaw/references/hrea1985.htm), and the USDA Animal Welfare Regulations (http://www.nal.usda.gov/awic/legislat/usdaleg1.htm), as applicable.

HUMAN SUBJECTS PROTECTION: Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained. http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm

DATA AND SAFETY MONITORING PLAN: Data and safety monitoring is required for all types of clinical trials, including physiologic, toxicity, and dose-finding studies (phase I); efficacy studies (phase II); efficacy, effectiveness and comparative trials (phase III). The establishment of data and safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risk to the participants. (NIH Policy for Data and Safety Monitoring, NIH Guide for Grants and Contracts, June 12, 1998: http://grants.nih.gov/grants/guide/notice-files/not98-084.html).

SHARING RESEARCH DATA: Investigators submitting an NIH application seeking $500,000 or more in direct costs in any single year are expected to include a plan for data sharing or state why this is not possible. http://grants.nih.gov/grants/policy/data_sharing Investigators should seek guidance from their institutions, on issues related to institutional policies, local IRB rules, as well as local, state and Federal laws and regulations, including the Privacy Rule. Reviewers will consider the data sharing plan but will not factor the plan into the determination of the scientific merit or the priority score.

INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH: It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing clinical research should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research - Amended, October, 2001," published in the NIH Guide for Grants and Contracts on October 9, 2001 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html; a complete copy of the updated Guidelines are available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical

trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS: The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects that is available at http://grants.nih.gov/grants/funding/children/children.htm

REQUIRED EDUCATION ON THE PROTECTION OF HUMAN SUBJECT PARTICIPANTS: NIH policy requires education on the protection of human subject participants for all investigators submitting NIH proposals for research involving human subjects. You will find this policy announcement in the NIH Guide for Grants and Contracts Announcement, dated June 5, 2000, at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

HUMAN EMBRYONIC STEM CELLS (hESC): Criteria for federal funding of research on hESCs can be found at http://stemcells.nih.gov/index.asp and at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html. Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (see http://escr.nih.gov). It is the responsibility of the applicant to provide, in the description and elsewhere in the application as appropriate, the official NIH identifier(s) for the hESC line(s) to be used in the proposed research. Applications that do not provide this information will be returned without review.

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT: The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm.

Applicants may wish to place data collected under this RFA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

STANDARDS FOR PRIVACY OF INDIVIDUALLY IDENTIFIABLE HEALTH INFORMATION: The Department of Health and Human Services (DHHS) issued final modification to

the “Standards for Privacy of Individually Identifiable Health Information”, the “Privacy Rule,” on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the DHHS Office for Civil Rights (OCR).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR website (http://www.hhs.gov/ocr/) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on “Am I a covered entity?” Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html.

URLs IN NIH GRANT APPLICATIONS OR APPENDICES: All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

HEALTHY PEOPLE 2010: The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This RFA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.healthypeople.gov

AUTHORITY AND REGULATIONS: This program is described in the Catalog of Federal Domestic Assistance at http://www.cfda.gov/ and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under authority of the Superfund Amendments and Reauthorization Act of 1986, Title 1, Section III, and Title II, Section 209 (Public Law 99-499); and are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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